REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1, 3, 5, 7, 9-14 presently appear in this application, with claims 13-14 being withdrawn by the examiner, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

It is noted that the examiner indicated in the Office Action of May 27, 2003, Paper No. 16, that claims 13-15 have been cancelled. Applicants wish to point out for the record that claims 13 and 14 are simply withdrawn.

The examiner states that the rejection of claims 9-12 and 16 under 35 U.S.C. §101, as set forth at pages 3-4 of Paper No. 14, remains. The examiner indicates that applicants' arguments have been fully considered but is not deemed to be persuasive because both Muzio et al. and Colotta et al. teach that icIL-1ra-II is mostly intracellular. It is the examiner's position that the possibility that icIL-1ra-II is glycosylated cannot be totally excluded and therefore it is necessary to use the word "isolated" or "purified" to modify glycosylated icIL-1ra-II in order to avoid having the claims read on a product of nature.

Applicants wish to point out to the examiner that it is the examiner's burden to establish that the intracellular protein

is glycosylated in order for this rejection to be proper. However, in deference to the examiner's suggestion and in order to advance prosecution, claims 9 and 16 are amended to recite "isolated" glycosylated icIL-1ra-II, thereby obviating this rejection.

Claims 1-12 and 16 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Pecceu et al. and Bjorkdahl et al. in view of Muzio et al. for the reasons set forth at pages 4-6 of the previous Office Action, Paper No. 14.

While applicants do not agree with the examiner's position, this issue is made moot by the amendment to claim 1 to recite that the DNA segment encoding a genomic growth hormone signal peptide with an intron and that the icIL-1ra-II produced has the amino acid sequence of SEQ ID NO:11 at the N-terminus. The amendment to claim 1 is supported in the specification at page 1, lines 9-10, for "DNA expression vectors containing genomic DNA sequence of the human growth hormone (hGH) signal peptide", Fig. 1A for showing the intron sequence in the middle of the sequence encoding the growth hormone signal peptide (GHsp), and page 17, lines 15-18.

At the time of filing the application, it was known in the art that the cleavage of the signal peptide and protein secretion not only depends on the sequence of the signal peptide itself, but also depends on the residues +1 and +2 of the protein

of interest (see von Heijn, Nucl. Acids. Res. 1986 reference attached hereto). For example, correct cleavage at residue +1A in Il-1 is predicted to occur if the growth hormone signal peptide (GHsp) is fused to the mature IL-1 (see Figure 1 attached hereto). In contrast, non-homogenous cleavage (at 3 different sites at residues +1M (15%), +3L (25%) and +5D (55%)) resulting in a non-homogeneous protein preparation is predicted using the same GH signal peptide with mature icIL-1ra-II (Figure 2 attached hereto). Moreover, the substitution of the insulin signal peptide for GHsp in both proteins results in essentially the same prediction, i.e., the homogeneous cleavage at residue +1A in IL-1 (Figure 3 attached hereto), and non-homogenous cleavage (Figure 4 attached hereto) in icIL-1ra-II.

Applicants unexpectedly found that by fusing the sequence of icIL-1ra-II to the genomic growth hormone signal peptide, a secreted fully glycosylated active protein starting at amino acid +2A is obtained (Example 10, page 17). Such an unexpected result, in which the icIL-1ra-II protein starts at +2A instead of the predicted mixture of proteins starting at of +1M, +3L and +5D, as discussed above, was obtained because, in contrast to the cited and applied references, the DNA encoding the growth hormone signal peptide used in the expression vector is genomic and therefore contains the sequence of the first intron of the human growth hormone gene. Accordingly, the cited

and applied references cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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